WEST

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L19: Entry 24 of 50 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5981505 A
TITLE: Compositions and methods for delivery of genetic material

Detailed Description Text (379):
The Tat protein is a transactivator of LTR-directed gene expression. It is absolutely essential for HIV replication. Tat is produced early in the viral replication cycle and functional Tat is required for expression of Gag, Pol, Env and Vpr. The predominant form of Tat is an 86-amino acid protein derived from two exon mRNAs. The amino-terminal 58 amino acids are sufficient for transactivation, although with reduced activity. Tat acts on a cis-acting sequence termed tar, to produce a dramatic increase in LTR-driven gene expression. Tat may act in part through increased RNA synthesis and in part by increasing the amount of protein synthesized per RNA transcript. Until recently, Tat was thought to act only on the HIV-1 LTR. However, Tat-activated expression from the JC virus late promoter has also been reported. Tat may also stimulate cell proliferation as an exogenous factor, and may play a contributory role in promoting the growth of Kaposi's Sarcoma in HIV-infected individuals. Because of such potentially detrimental effects in both HIV-infected and -noninfected individuals, preferred tat constructs employed for genetic immunization are modified to express only non-functional Tat. Mutations capable of inactivating Tat or Rev can in addition act as transdominant mutations, thereby potentially inactivating any functional Tat being produced in an HIV-infected individual.

WEST Search History

DATE: Wednesday, October 16, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=ADJ			
L19	L18 with l17	50	L19
L18	construct or plasmid or vector	224911	L18
L17	L16 with l15	108	L17
L16	hiv or lentivi$	15882	L16
L15	l13 with l14	179	L15
L14	lack or lacking or defec$ or non-functional or mutated or disrupted	424070	L14
L13	tat	9148	L13
L12	5994136.pn.	1	L12
L11	gag with endogenous with upstream	3	L11
L10	5994136	5	L10
L9	6218187	1	L9
L8	6156728	1	L8
L7	6051427	1	L7
L6	6013516	6	L6
L5	5994136	5	L5
L4	5858740	3	L4
L3	5834256	7	L3
L2	5686279	15	L2
L1	6428953	1	L1

END OF SEARCH HISTORY

L7 ANSWER 1 OF 6 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
AN 1999-06872 BIOTECHDS
TI DNA immunization with **HIV**-1 tat mutated in the trans activation domain induces humoral and cellular immune responses against wild-type tat;
HIV virus-1 mutant tat nucleic acid **vaccine**
AU Caselli E; Betti M; Grossi M P; Balboni P G; Rossi C; Boarini C; Cafaro A; Barbanti-Brodano G; Ensoli B; *Caputo A
CS Univ.Ferrara; Inst.Super.Health-Rome
LO Department of Experimental and Diagnostic Medicine, Section of Microbiology, University of Ferrara, Via Luigi Borsari 46, I-44100 Ferrara, Italy.
Email: cpa@dns.unife.it
SO J.Immunol.; (1999) 162, 9, 5632-38
CODEN: JOIMA3 ISSN: 0022-1767
DT Journal
LA English
AB Plasmid DNA encoding two **transdominant** negative mutants of the **HIV** virus-1 Tat protein (Tat22 and Tat22/37) were immunized i.m. into mice (using plasmid pC-tat22 and plasmid pC-tat22/37) which resulted in a humoral response to wild-type Tat comparable to that induced by inoculation of wild-type tat DNA or Tat protein. There was no difference between antibody titers, which continued to rise after 3 additional DNA boosts between mice treated with mutant or wild-type tat genes. Anti-tat IgG antibodies were found in mice immunized with tat DNA constructs, in contrast to mice immunized with the Tat protein in which different Tat epitopes were detected. Sera from most of the immunized mice neutralized the effect of extracellular Tat in activating **HIV** virus-1 replication. Wild-type tat also stimulated the proliferation of splenocytes. Wild-type antigen was recognized by antibodies and T-lymphocytes induced by DNA immunization with mutated tat genes. Tat **transdominant** mutants, lacking viral transactivation activity and capable of blocking wild-type Tat activity may be useful for developing a **HIV** virus-1 **vaccine**. (67 ref)

L7 ANSWER 4 OF 6 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
AN 1996-02742 BIOTECHDS
TI Immune-based therapies for treatment of **HIV** infection; including recombinant **vaccine**, immunotherapy, intracellular immunization and gene therapy strategies; a review
AU Piscitelli S C; Minor J R; Saville M W; Davey Jr R T
CS Nat.Inst.Health-Bethesda; Nat.Inst.Allergy+Infec.Dis.Bethesda; Univ.California
LO Department of Pharmacy, Warren G Magnuson Clinical Center, National Institutes of Health, Building 10, Room 1N257, Bethesda, MD 20892, USA.
SO Ann.Pharmacother.; (1996) 30, 1, 62-76
CODEN: APHRER ISSN: 1060-0280
DT Journal
LA English
AB In vitro, animal and clinical data on immunotherapy strategies for **HIV** infection are reviewed, with respect to: laboratory monitoring of immune-based therapies; immune-based agents (interleukin-2, interleukin-4, interleukin-12, interleukin-10, interferon-alpha, immunotoxins, inflammatory cytokine-inhibitors and recombinant **vaccine** candidates); obstacles to **vaccine** development; animal models; **vaccine** studies in humans; and gene therapy. Candidate vaccines include recombinant envelope glycoproteins (gp120 and gp160), live non-**HIV** recombinant virus vectors (e.g. pox virus) and attenuated virus. Gene therapy strategies include: insertion of novel genes into human cell lines for intracellular immunization and blocking of viral replication, e.g. by **transdominant** negative interference, combination of an **HIV** rev gene with a diphtheria toxin gene, or a ribozyme approach; adoptive cytotoxic T-lymphocyte transfer after modification for enhanced **HIV**-infected cell killing; use of **HIV** vectors (giving host cell specificity); and gene transfer to hematopoietic stem cells. (145 ref)

L12 ANSWER 1 OF 2 CANCERLIT
AN 90665936 CANCERLIT
DN 90665936
TI **HIV** AND AIDS: PATHOGENESIS, THERAPY AND VACCINE.
AU Anonymous
CS No affiliation given.
SO J Cell Biochem, (1990) (Suppl 14D) 77-181.
ISSN: 0730-2312.
DT Book; (MONOGRAPH)
LA English
FS Institute for Cell and Developmental Biology
EM 199101
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB A symposium on **HIV** and AIDS, part of the UCLA series, was held in Keystone, Colorado, from March 31 to April 6, 1990. The symposium covered **HIV** regulation and pathogenesis; cellular targets for **HIV** infection; genetic and biologic variants of **HIV**; pathogenic mechanisms and immune responses in **HIV**; molecular targets for therapy; primate/animal models of AIDS; candidate vaccines and clinical trials; Kaposi's sarcoma and other AIDS-associated malignancies; human T lymphotropic virus-I and other virus cofactors; **HIV** genes and gene products; cellular and viral (non-**HIV**) factors that influence **HIV** production; **HIV**-related viruses and animal models; serology, immunology, and cell biology; and AIDS vaccine and treatment. Specific topics include replication and pathogenesis of **HIV**-1, structural organization and regulation of expression of **HIV**-1, **HIV** regulatory genes, envelope glycoproteins of **HIV**-1, epidemiology and natural history of **HIV**-2, immunopathogenesis of **HIV** infection, **HIV** in hematopoiesis, immune reactivity of **HIV** (damaging or beneficial to the host?), gene therapy for AIDS, interaction of the **HIV** envelope with the human CD4 receptor, regulation of gene expression in animal and primate lentiviruses, immunobiology of the **HIV** envelope, biosynthesis and assembly of recombinant **HIV** proteins, the effects of dideoxynucleosides on **HIV** infection, molecular interaction of **HIV** and human cytomegalovirus, limited DNA diversity in **HIV**-1 isolates obtained from close contacts, detection of **HIV**-1 proviral sequences in liver cells, retrovirus-mediated transfer of **tat** and rev genes of **HIV**, **nonessential** genes of **HIV**-1, processing of the gag precursor of **HIV**, toxin gene regulation by **HIV**-1 **tat** and rev, polymerase chain reaction standardization program, expression of **HIV**-1 protein and mRNA in lymphoid tissue after **HIV** infection, electron microscopic visualization of **HIV** reverse transcriptase, effect of recombinant lymphokines on naturally **HIV**-1-infected CD4+ T cells in vitro, cellular proteins that react with the negative regulatory element of the **HIV**-1 long-terminal repeat, modulation of **HIV**-1 multiplication by recombinant interferon-alpha 2 and azidothymidine treatment of monocytic cells, cytokine gene expression during **HIV**-1 infection of monocytic cells, and possible association between **HIV** infection in monocytes and the monocyte cell surface antigens CD13 and CD14.

L16 ANSWER 9 OF 28 MEDLINE DUPLICATE 3
AN 1998440501 MEDLINE
DN 98440501 PubMed ID: 9765382
TI A third-generation lentivirus vector with a conditional packaging system.
AU Dull T; Zufferey R; Kelly M; Mandel R J; Nguyen M; Trono D; Naldini L
CS Cell Genesys, Foster City, California 94404, USA.
SO JOURNAL OF VIROLOGY, (1998 Nov) 72 (11) 8463-71.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199811
ED Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981105
AB Vectors derived from human immunodeficiency virus (HIV) are highly efficient vehicles for in vivo gene delivery. However, their biosafety is of major concern. Here we exploit the complexity of the HIV genome to provide lentivirus vectors with novel biosafety features. In addition to the structural genes, HIV contains two regulatory genes, **tat** and rev, that are essential for HIV **replication**, and four accessory genes that encode critical virulence factors. We previously reported that the HIV type 1 accessory open reading frames are dispensable for efficient gene transduction by a lentivirus vector. We now demonstrate that the requirement for the **tat** gene can be offset by placing constitutive promoters upstream of the vector transcript. Vectors generated from constructs containing such a chimeric long terminal repeat (LTR) transduced neurons in vivo at very high efficiency, whether or not they were produced in the presence of **Tat**. When the rev gene was also **deleted** from the packaging construct, expression of **gag** and **pol** was strictly dependent on Rev complementation in trans. By the combined use of a separate nonoverlapping Rev expression plasmid and a 5' LTR chimeric transfer construct, we achieved optimal yields of vector of high transducing efficiency (up to 10(7) transducing units [TU]/ml and 10(4) TU/ng of p24). This third-generation lentivirus vector uses only a fractional set of HIV genes: **gag**, **pol**, and rev. Moreover, the HIV-derived constructs, and any recombinant between them, are contingent on upstream elements and trans complementation for expression and thus are nonfunctional outside of the vector producer cells. This split-genome, conditional packaging system is based on existing viral sequences and acts as a built-in device against the generation of productive recombinants. While the actual biosafety of the vector will ultimately be proven in vivo, the improved design presented here should facilitate testing of lentivirus vectors.